CHAPTER III

OXIDATION OF MIXTURES OF UNSYMMETRICAL 1,3-DIALKYLTHIOUREAS
AND THIOUREA

INTRODUCTION

The results obtained from the oxidation of mixtures of thioureas described in the previous chapter has shown that in the intermediate bis(formamidino) sulphide dihydrochloride containing one N,N'-dialkylamidino group and one unsubstituted amidino group, the migration of the latter to the former is observed during the isomerisation to the amidinothiourea. In the case of oxidation of a mixture of unsymmetrical 1,3-diarylthiourea and thiourea, the migration of the unsubstituted amidino group in the bis(formamidino) sulphide dihydrochloride (not isolated) was found to occur on to the nitrogen which carried the more electron releasing aryl group. To study the effect of steric as well as electronic factors of the different alkyl groups on the isomerisation of bis(formamidino) sulphide to amidinothiourea, oxidation of mixtures of unsymmetrical 1,3-dialkylthioureas and thiourea was carried out. It was thought that any effect of the bulk and the inductive effect of the group
on the migration behaviour might become apparent from these experiments. In most of the cases studied, benzyl group was chosen as the fixed alkyl moiety because in its steric effect it lies in between ethyl and isopropyl group. 182

The oxidation could lead to a single product or to a mixture of products. The latter would be the case if the electronic effect and the bulkiness of the group are important controlling factors. The structure identification of the thiadiazole and the amidinothiourea would throw light on the migration terminus and on the migrating group. This oxidation would also involve the formation of bis(formamidino) disulphides (1) or (2 and 3), bis(formamidino) sulphide (4) and amidinothiourea salts (5) or (6) as intermediates. If the migration is onto the unsubstituted nitrogen, the amidinothioureas formed would be either (9) or (10) which in turn could cyclise to the thiadiazole (11) and (12). However in no case studied so far, such a course of reaction has been observed and hence the formation of amidinothiourea with structure (9) or (10) appeared unlikely.
\[
\text{RNH-C-NHR}^1 + \text{H}_2\text{N-C-NH}_2 \rightarrow \text{RNH-C-S-S-C-NH}_2\cdot2\text{HCl} \tag{1}
\]

and/or
\[
\text{RNH-C-S-S-C-NHR}^1 \cdot 2\text{HCl} + \text{H}_2\text{N-C-S-S-C-NH}_2\cdot2\text{HCl} \tag{2}
\]

\[
\text{RN=CN}^1 \rightarrow \text{RN=CN}^1 \cdot \text{HCl} \rightarrow \text{RNH-C-NHR}^1 + \text{NH}_2\text{CN} \rightarrow \text{RNH-C-NHR}^1 + \text{NH}_2\text{CN} \rightarrow \text{RNH-C-S-S-C-NH}_2\cdot2\text{HCl} \tag{4}
\]

\[
\text{RNH-C-NR}^1 \cdot \text{C-NH}_2\cdot\text{HCl} \text{ or } \text{RNH-C-NR}^1 \cdot \text{C-NH}_2\cdot2\text{HCl} \tag{5}
\]

(a) \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2^- \) \quad \text{CH}_3\text{CH}_2\text{CH}_2^-

(b) \( \text{C}_6\text{H}_5\text{CH}_2 \)

(c) \( \text{C}_2\text{H}_5 \)

(d) \( \text{CH}_3\text{CH}_2\text{CH}_2^- \)

(e) \( \text{CH}_3\text{(CH)}\text{CH}_3 \)

(f) \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2^- \)
RESULTS AND DISCUSSIONS

The oxidations were carried out as detailed in Chapter II. The number of compounds in the crude product mixture were determined by thin layer chromatography. The chromatogram showed that in the oxidation of mixtures of thioureas, apart from the products arising from the oxidation of 1,3-dialkylthioureas only one other compound was formed, presumably the product incorporating one molecule each of the two different thioureas used. This product could easily be separated from others by extraction with dilute acid.

The base obtained as the product of oxidation of a mixture of 1-\(\text{n}\)-butyl-3-\(\text{n}\)-propylthiourea and thiourea was found to have a molecular composition \(\text{C}_9\text{H}_{18}\text{N}_4\text{S}\) from elemental analysis. The base shows strong absorptions due to C=N and NH stretching modes of vibration at 1620 and 3150 cm\(^{-1}\) respectively. Hydrogen sulphide in acidic solution was
found to open this thia diazole ring. The product of reduction could not be isolated, however. The reduction product in solution in presence of sodium bicarbonate decomposed to give butyl isothiocyanate. This indicates that the amidinothiourea has a 1-amidino-3-butyl-1-n-propylthiourea structure and consequently the base is 3-amino-5-n-butylimino-4-n-propyl-4,5-dihydro-1,2,4-thiadia zole. The solution obtained after reduction when oxidised with hydrogen peroxide gave back the same thiadia zole.

\[
\begin{align*}
\text{n-PrN} & \text{C-NH}_2 \\
\text{n-BuN} & \text{C} \quad \text{S} \\
\text{N} & \\
\text{Pr-n} & \\
\text{c-s} & \\
\text{Pr-n} & \text{NH} \\
\text{N} & \\
\text{NH} & \\
\end{align*}
\]

\[(7a)\]

\[
\text{n-BuNCS} + \text{n-PrNH-C-NH}_2
\]

The base formed from the oxidation of a mixture of 1-benzyl-3-methylthiourea and thiourea has an elemental composition \(\text{C}_{10}\text{H}_{12}\text{N}_4\text{S}\) from analysis and molecular weight determination (mass spectrometric). The base shows strong i.r. absorptions at 3500 and 3200 cm\(^{-1}\) due to NH stretching vibrations and at 1640 cm\(^{-1}\) due to C=N vibrations. In its n.m.r. spectrum, apart from aryl proton signal, there are broad singlet of NH\(_2\) group at \(\delta 4.8\), another singlet due to
two protons of benzyl group at $\delta$ 4.28 and a sharp singlet of methyl group at $\delta$ 3.32. In 3,5-diarylimino-2,4-dimethyl-1,2,4-thiadiazolidines the signal due to the methyl group at four position was always found to be at $\delta$ 3.4-3.42. Hence it is possible that the methyl group in the above thiaodiazole is at four position.

The following chemical evidence in the form of degradation studies also suggests the structure 3-amino-5-benzylimino-4-methyl-4,5-dihydro-1,2,4-thiadiazole. The amidinothiourea obtained by reduction was decomposed by warming in sodium bicarbonate solution when it gave benzyl isothiocyanate and methylguanidine. The formation of methylguanidine along with benzyl isothiocyanate suggests that the amidinothiourea formed is 1-alkyl-1-amidino-3-benzylthiourea (5; $R = $ benzyl, $R^1 = $ Me).

The product obtained by the oxidation of 1-benzyl-3-ethylthiourea and thiourea has a composition $C_{11}H_{14}N_4S$. Its reduction with hydrogen sulphide in hydrochloric acid solution gave a pale yellow solution which decomposed in presence of sodium bicarbonate into benzylguanidine and
ethyl isothiocyanate. As observed in the earlier cases, the solution obtained after reduction could be oxidised back to the thiadiazole. Hence the structure of the thiadiazole should be 3-amino-4-benzyl-5-ethylimino-4,5-dihydro-1,2,4-thiadiazole. In the n.m.r. spectrum of the base, the N4 benzylmethylene protons are found to give a signal at δ 5.0. In the product obtained from the oxidation of 1-benzyl-3-methylthiourea and thiourea, methylene protons of the benzyl group at 5 position absorbs at δ 4.28. Clearly this supports the positional difference for the benzyl group in the thiadiazoles. It is noteworthy that in 3-amino-4-benzyl-5-benzylimino-4,5-dihydro-1,2,4-thiadiazole (Chapter II), the methylene protons of the two benzyl groups absorb respectively at δ 4.2 and δ 5. Therefore by comparison of these values with the absorption value of the above two bases (7b) and (7c), the absorption at δ 5.0 can be assigned to the N4 benzyl group and the one at δ 4.2 to the C5 benzylimino group in the dibenzyl substituted analogue. (see Fig.1 & 2).

The oxidation of binary mixtures of 1-benzyl-3-n-propylthiourea and thiourea, 1-benzyl-3-isopropylthiourea and thiourea, 1-benzyl-3-n-butylthiourea and thiourea also gave thiadiazoles which behaved similarly in that they all gave benzylguanidine and the alkylisothiocyanate, when the
Fig. 1
respective amidinothioureas obtained by reduction was decomposed with sodium bicarbonate. Therefore, in all these thiadiazoles the benzyl group was assigned to the N4 nitrogen. The n.m.r. spectra of these thiadiazoles showed the methylene protons of the benzylic group consistently in the range $\delta$ 5.0-5.1. This also confirms the fact that in these thiadiazoles the benzyl group is on N4 nitrogen of the ring.

The bases obtained from these oxidations formed monopicrates. They did not form any benzoyl derivative under Schotten-Baumann conditions. The bases did not form any condensation products with phenyl isothiocyanate or carbon disulphide also. They were found to be stable in boiling 3N acid and alkali and could not be desulphurised with alkaline lead acetate. The non-reactivity of these amino derivatives towards acylation or addition with heterocumulenes parallels that of 3-amino-4-aryl-5-aryl(alkyl)-imino-4,5-dihydro-1,2,4-thiadiazole.\textsuperscript{117,120}

Interaction of cyanamide and unsymmetrical 1,3-dialkylthioureas or the corresponding carbodiimides and thiourea in acetone medium in presence of hydrochloric acid yielded the related bis(formamidino) sulphide dihydrochlorides. These compounds were identified as bis(formamidino) sulphide dihydrochlorides by their reductive cleavage to 1,3-dialkylthioureas and thiourea with hydrogen sulphide. It was also
found that these compounds did not yield any isothiocyanate on treatment with sodium bicarbonate; instead carbodiimides were formed. Besides, oxidation of these hydrochlorides failed to yield any thiadiazoles. The bis(formamidino) sulphide dihydrochloride underwent isomerisation to amidinothiourea by refluxing in ethanol for 2 hrs. The amidinothiourea so formed in solution on decomposition with sodium bicarbonate solution gave benzylguanidine and alkyl isothiocyanate in the case of products obtained from 1-benzyl-3-ethylthiourea, 1-benzyl-3-\( n \)-propylthiourea, 1-benzyl-3-isopropylthiourea or 1-benzyl-3-\( n \)-butylthiourea. Therefore the structure of these amidinothioureas could only be formulated as (5c-f). Methylguanidine and benzyl isothiocyanate are the degradation products obtained from the amidinothiourea formed by the isomerisation of the bis-(formamidino) sulphide dihydrochloride \( (4; \text{R} = \text{benzyl}, \text{R}^1 = \text{Me}) \). Therefore the amidinothiourea in this case is formulated as \( (5b; \text{R} = \text{benzyl}, \text{R}^1 = \text{Me}) \). The decomposition of the amidinothiourea obtained by the isomerisation of bis(formamidino) sulphide dihydrochloride \( (4a; \text{R} = \text{butyl}, \text{R}^1 = \text{propyl}) \) gave butyl isothiocyanate and \( n \)-propylguanidine (not isolated).

The results obtained from these oxidations show that the migrating moiety in the bis(formamidino) sulphide dihydrochloride is the unsubstituted amidino group. Further, it is
observed that in the case of bis(formamidino) sulphide dihydrochloride (4b; R = Me, R' = benzyl), the unsubstituted amidino part migrated to the methyl nitrogen. In all the other alkyl-benzyl derivatives, the migration occurred onto the nitrogen bearing benzyl group and in the \( \text{n-butyl-n-propyl} \) derivative the migration occurred on to the nitrogen bearing the \( \text{n-propyl} \) group. It can be concluded that the +I effect of the substituent as well as steric factor has some effect on the mode of isomerisation.

In the bis(formamidino) sulphide dihydrochloride, the nitrogen which carried the more electron releasing substituent on the amidino part was likely to get protonated and hence the unsubstituted amidino part migrated to the non-protonated nitrogen. Thus in benzyl-ethyl, benzyl-propyl,
benzyl-butyl and benzyl-isopropyl derivatives, it was the nitrogen which carried the benzyl group which is the non-protonated one and hence the unsubstituted amidino part migrated onto that nitrogen. In benzyl-methyl (4b; \( R = \text{benzyl}, R^1 = \text{Me} \)) and \( n\)-butyl-\( n\)-propyl (4a; \( R = \text{butyl}, R^1 = \text{propyl} \)) derivatives, the mode of isomerisation was controlled by the steric factor. The positive effect of \( n\)-propyl and \( n\)-butyl does not vary much and so it was probably the steric factor which was more operative here.

EXPERIMENTAL

Unsymmetrical 1,3-dialkylthioureas were prepared by the condensation of alkylisothiocyanates with alkylamine.\(^{179}\) The purity of all new compounds reported in this chapter was verified by t.l.c. experiments.

I. OXIDATION OF MIXTURES OF UNSYMMETRICAL 1,3-DIALKYLTHIOUREAS AND THIOUREA: FORMATION OF 4-ALKYL-5-ALKYLIMINO-3-AMINO-4,5-DIHYDRO-1,2,4-THIADIAZOLES

a) 3-Amino-5-\( n\)-butylimino-4-\( n\)-propyl-4,5-dihydro-1,2,4-thiadiazole

A mixture of 1-\( n\)-butyl-3-\( n\)-propylthiourea (8.7g, 0.05 mol) and thiourea (3.8g, 0.05 mol) were suspended in 1:1 ethanol-water mixture (150 ml) containing concentrated
hydrochloric acid (11.5 ml, 32%, 0.1 mol). Hydrogen peroxide (11.5 ml, 30%, 0.1 mol) was added gradually with stirring. The reaction mixture was then kept at 80-90° for two hours.

After cooling to room temperature, the precipitated sulphur was removed by filtration and the reaction mixture was poured into ice-cold ammonia solution. After some time it was reacidified and the oily layer which remained undissolved was extracted with benzene. The aqueous acidic solution on basification afforded white precipitate (3g, 28%) which on crystallisation to constant melting point from benzene-petroleum ether mixture gave colourless shining plates of 3-amino-5-n-butylimino-4-n-propyl-4,5-dihydro-1,2,4-thiadiazole, m.p. 90°. (Found: C,50.7; H,8.4; N,26.3; S,15.1. C₉H₁₈N₄S requires C,50.5; H,8.4; N,26.1; S,14.9%). v max (KBr) 3150s (NH); 1660s (NH₂ def); 1620s (C= N); 1460s (CH alkyl) cm⁻¹. N.m.r. (CDCl₃): δ 0.8-1.2, m, 6 aliphatic H; 1.2-2.0, m, 6 aliphatic H; 3.1, m, 2 methylene H of N₄-CH₂CH₂CH₃; 3.7, m, 2 methylene H of C₅-NCH₂CH₂CH₂CH₃; 4.8, s, 2 amino H.

To verify the product obtained from the oxidation of mixtures of 1-n-butyl-3-n-propylthiourea and thiourea contained any other products, a chromatogram was developed as follows in petroleum ether. After the oxidation of the
binary mixtures of thioureas the solution was basified and the products formed were extracted with benzene. This benzene extract was used for t.l.c. The product obtained by the oxidation of 1-\textsuperscript{n}-butyl-3-\textsuperscript{n}-propylthiourea alone also, after basification and extraction with benzene was subjected to t.l.c. and the chromatograms were compared. The first one showed only one additional spot and this was due to the product derived from 1-\textsuperscript{n}-butyl-3-\textsuperscript{n}-propylthiourea and thiourea.

To an aqueous acidic solution of the base, picric acid was added. The picrate obtained was crystallised from ethanol as shining needles, m.p. 111°. (Found: N,21.5; S,6.9. \( C_{9}H_{18}N_{4}S \cdot C_{6}H_{3}N_{3}O_{7} \) requires N,22.1; S,7.2%).

b) 3-Amino-5-benzylimino-4-methyl-4,5-dihydro-1,2,4-thiadiazole (7b)

To a solution of 1-benzyl-3-methylthiourea (9g, 0.05 mol) and thiourea (3.8g, 0.05 mol) in ethanol (50 ml) containing concentrated hydrochloric acid (11.5 ml, 32%, 0.1 mol), hydrogen peroxide (11.5 ml, 30%, 0.1 mol) was added gradually with stirring. The mixture, after the addition of the oxidant, was warmed at 60-70°C for one hour. The solution, after removal of precipitated sulphur, was then poured into crushed ice containing concentrated ammonia (10 ml). The coagulated white solid thus obtained was collected and
extracted with dilute hydrochloric acid (0.025 N, 100 ml). The acidic extract on basification yielded a white powder which was collected and dried (2.9 g, 26.4%). It crystallised from benzene-petroleum ether mixture as shining leaflets; m.p. 142°. (Found: C, 54.6; H, 5.5; N, 25.5; S, 14.6%.

C_{10}H_{12}N_{4}S requires C, 54.5; H, 5.5; N, 25.5; S, 14.6%).

$\gamma_{\text{max}}$ (KBr) 3500 s, 3200 s (NH); 1640 s (C=N); 1580 m (C=C aryl); 1480 s (CH alkyl); 780 m, 720 m (Ph) cm$^{-1}$. N.m.r. (CDCl$_3$); $\delta$ 3.32, s, 3 methyl H; 4.28, s, 2 methylene H of benzyl; 4.8, s, 2 amino H. 7.25-7.40, m, 5 aromatic H. Mass spectrum; m/e(%): 221 (9); 220 (56); 219 (20); 205 (4), 143 (13), 115 (15), 92 (77), 91 (100); 77 (8), 74 (6), 73 (9), 65 (15), 57 (14).

In this case also a chromatogram was developed with the benzene extract obtained after the basification of the reaction mixture. Similarly another was developed for the product obtained from the oxidation of 1-benzyl-3-methylthiourea alone. The former chromatogram showed only one intense additional spot corresponding to the 'mixed' product when compared with the latter.

A dilute hydrochloric acid solution of the base, when mixed with aqueous picric acid solution, precipitated a picrate which on crystallisation from ethanol gave yellow needles, m.p. 108°. (Found: N, 21.4; S, 7.3. C$_{10}$H$_{12}$N$_{4}$S.

C$_6$H$_3$N$_3$O$_7$ requires N, 21.8; S, 7.1%).
c) 3-Amino-4-benzyl-5-ethylimino-4,5-dihydro-
1,2,4-thiadiazole (7c)

The oxidation of 1-benzyl-3-ethylthiourea (9.7g, 0.05 mol) and thiourea (3.8g, 0.05 mol) on working up as described in above experiment yielded a white powder (3.5g, 29.9%). This on crystallisation from benzene-petroleum ether yielded shining plates of (7c) m.p. 156°. (Found: C, 56.4; H, 6.1; N, 23.7; C$_{11}$H$_{14}$N$_4$S requires C, 56.4; H, 5.98; N, 23.9; S, 13.7%). $\nu$ max (KBr) 3350s, 3200s (NH); 1660m (NH$_2$ def); 1620s (C=N); 1580s (C=C aryl); 1480s (CH alkyl); 740m (Ph) cm$^{-1}$. N.m.r. (CDCl$_3$): $\delta$ 1.25, t, 3 methyl H; 3, quartet, 2 methylene H; 4.6, s, 2 amino H; 5.0, s, 2 methylene H of N$_4$-CH$_2$C$_6$H$_5$; 7.3, m, 5 aromatic H. Mass spectrum: m/e (%): 235(8); 234(53); 219(6); 205(11); 143(38); 101(8); 91(8); 91(100); 65(13); 44(6); 43(7); 39(5). Ficrate, needles from ethanol, m.p. 181°. (Found: N, 20.8; S, 6.4. C$_{11}$H$_{14}$N$_4$S. C$_6$H$_3$N$_3$O$_7$ requires N, 21.2; S, 6.9%).

d) 3-Amino-4-benzyl-5-n-propylimino-4,5-dihydro-
1,2,4-thiadiazole (7d)

The oxidation of 1-benzyl-3-n-propylthiourea (10.4g, 0.05 mol) and thiourea (3.8g, 0.05 mol) afforded 7d (3.5g, 28.2%) which on crystallisation from benzene-petroleum ether mixture gave shining plates, m.p. 138°. (Found: C, 57.6; H, 6.2; N, 22.7; S, 12.7. C$_{12}$H$_{16}$N$_4$S requires C, 58.1; H, 6.5;
N, 22.6; S, 12.9%). $\nu_{\text{max}}$ (KBr): 3280s, 3140s (NH); 2960m (CH stretch); 1670s (NH$_2$ def); 1620s (C=N); 1570s, 1495s (C=C aryl); 1470s (C-H alkyl); 730s (Ph) cm$^{-1}$. N.m.r. (CDCl$_3$): $\delta$ 0.9, t, 3 methyl H; 1.5-2.0, m, 2 methylene H; 3.1, t, 2 methylene H; 4.6, s, 2 amino H. 5.1, s, 2 methylene H of C$_5$-CH$_2$C$_6$H$_5$; 7.5-7.7, m, 5 aromatic H. Mass spectrum: m/e (%): 248(11); 219(10); 159(8); 92(8); 91(100); 65(16); 43(16). Picrate, needles from ethanol, m.p. 152°. (Found: N, 20.0; S, 6.5. C$_{12}$H$_{16}$N$_4$S. C$_6$H$_3$N$_3$O$_7$ requires N, 20.5; S, 6.7%).

e) 3-Amino-4-benzyl-5-isopropylimino-4,5-dihydro-1,2,4-thiadiazole (7e)

A solution of 1-benzyl-3-isopropylthiourea (10.4g, 0.05 mol) and thiourea (3.5g, 0.05 mol) in ethanol on oxidation gave 7e (3g, 24%). It was crystallised from benzene-petroleum ether mixture to obtain shining plates, m.p. 158°. (Found: C, 57.8; H, 6.6; N, 22.7; S, 12.6; C$_{12}$H$_{16}$N$_4$S requires C, 58.1; H, 6.5; N, 22.6; S, 12.9%). $\nu_{\text{max}}$ (KBr): 3300s, 3160s (NH); 2980m (CH stretch); 1665m (NH$_2$ def); 1620s (C=N); 1570s, 1495m, 1450s (C=C aryl) 1470s (CH alkyl); 730m (Ph) cm$^{-1}$. N.m.r. (CDCl$_3$): $\delta$ 1.15-1.35, d, 6 methyl H; 2.9-3.4, m, 1H; 4.4, s, 2 amino H; 5.1, s, 2 methylene H of CH$_2$C$_6$H$_5$; 7.3-7.5, m, 5 aromatic H. Picrate, needles from ethanol, m.p. 170°. (Found: N, 20.1; S, 6.3. C$_{12}$H$_{16}$N$_4$S. C$_6$H$_3$N$_3$O$_7$ requires, N, 20.5; S, 6.7%).
f) 3-Amino-4-benzyl-5-n-butylimino-4,5-dihydro-1,2,4-thiadiazole (7f)

The oxidation of 1-benzyl-3-n-butylthiourea (11.1g, 0.05 mol) and thiourea (3.8g, 0.05 mol) done as in the above case yielded 7f (4g, 30%) which on crystallisation from benzene-petroleum ether mixture afforded shining plates, m.p., 132°. (Found: C, 59.7; H, 7.0; N, 21.5; S, 12.0; C_{13}H_{18}N_{4}S requires C, 59.5; H, 6.9; N, 21.4; S, 12.2%).

υ_{max} (KBr) 3280s, 3125s (NH stretch); 1630m (NH_{2} def); 1610 (C=N); 1570s, 1500m, 1450s (C=C aryl); 1470s (CH alkyl); 730s (Ph) cm^{-1}. N.m.r. (CDCl_{3}); δ 0.8-1.1, m, 3 methyl H; 1.3-1.8, m, 4H; 3.1-3.9, t, 2 methylene H; 4.4, s, 2 amino H; 5.2, s, 2 methylene H of -CH_{2}C_{6}H_{5}; 7.5-7.7, m, 5 aromatic H.

Mass spectrum: m/e (%): 262 (10), 221(14.8), 173(8.6), 131(4); 130(5.3); 93(8.3), 92(5.6); 91(100); 65(12.2). Picrate, needles from ethanol, m.p. 130°. (Found: N, 19.6; S, 6.1.

C_{13}H_{18}N_{4}S. C_{6}H_{3}N_{3}O_{7} requires, N, 19.9; S, 6.5%).

II. REDUCTION OF 4-ALKYL-5-ALKYLIMINO-3-AMINO-4,5-DIHYDRO-1,2,4-THIADIAZoles

a) Reduction of 3-amino-5-n-butylimino-4-n-propyl-4,5-dihydro-1,2,4-thiadiazoles.

Hydrogen sulphide was bubbled through a solution of 3-amino-5-n-butylimino-4-n-propyl-4,5-dihydro-1,2,4-thiadiazole (3g) in dilute hydrochloric acid with occasional
warming. The bubbling of hydrogen sulphide was stopped when no further separation of sulphur was observed. No crystalline material could be separated on subsequent concentration and cooling.

The viscous solution was then diluted with water and divided into two portions and one portion was warmed with sodium bicarbonate solution for five minutes. It was then acidified with hydrochloric acid and steam distilled. The oily droplets obtained in the distillate was extracted with ether and then treated with ammonia, when needles of 1-butylthiourea (0.5g), m.p. 79° was obtained. Picric acid was added to the residual solution. No picrate was found to be formed. Possibly the propyl guanidine, which was formed underwent decomposition during steam distillation.

The other portion of the solution obtained after reduction was oxidised with hydrogen peroxide (1 ml, 30%) at room temperature and after some time basified with aqueous ammonia and cooled well. The product formed was crystallised from benzene-petroleum ether mixture when shining plates of (7a) was obtained, m.p. and m.m.p. 90°.

b) Reduction of 3-amino-5-benzylimino-4-methyl-4,5-dihydro-1,2,4-thiadiazole.

Through a hydrochloric acid solution of 3-amino-
5-benzylimino-4-methyl-4,5-dihydro-1,2,4-thiadiazole (4g), hydrogen sulphide was passed till the separation of sulphur was complete. Then one portion of the solution was warmed with sodium bicarbonate solution. The solution was then reacidified and extracted with ether. The extract was evaporated and the residual oil treated with ammonia when 1-benzylthiourea was obtained, m.p. and m.m.p. 162°.

To the solution obtained after extraction of benzyl isothiocyanate, picric acid was added. The picrate was identified as of methylguanidine, m.p. 200°. (Found: N,26.7. Calc. for C₂H₇N₃•C₆H₅N₃O₇: N,27.8%).

The remaining portion of the solution obtained after reduction was oxidised and worked up, when shining plates of 3-amino-5-benzylimino-4-methyl-4,5-dihydro-1,2,4-thiadiazole was formed, m.p. and m.m.p. 142°.

c) Reduction of 5-alkylimino-3-amino-4-benzyl-4,5-dihydro-1,2,4-thiadiazoles

The 5-alkylimino-3-amino-4-benzyl-4,5-dihydro-1,2,4-thiadiazoles were also reduced similarly. The products obtained after reduction and decomposition with sodium bicarbonate are listed in Table I.
III. FORMATION OF BIS(FORMAMIDINO) SULPHIDE DIHYDROCHLORIDES

a) Interaction of thioureas with cyanamide

1-\textit{n}-Butyl-3-\textit{n}-propylthiourea (8.7g, 0.05 mol) and cyanamide (2.1g, 0.05 mol) were mixed together in acetone (100 ml) and hydrogen chloride gas was passed through the well-stirred solution. A colourless crystalline material which separated was filtered, washed with acetone and dried (4a, 11.5g, 80%) m.p. 166°.

Other sulphide dihydrochlorides were prepared similarly and they are listed in Table II.

b) Interaction of unsymmetrical 1,3-dialkylcarbodiimides with thiourea.

In another experiment, 1-\textit{n}-butyl-3-\textit{n}-propylthiourea (8.7g, 0.05 mol) was dehydrosulphurised with yellow lead oxide. After filtration to remove lead sulphide and unreacted lead oxide, thiourea (3.8g, 0.05 mol) was added to the filtrate. On passing dry hydrogen chloride gas through the solution, a white crystalline substance was obtained. It was collected, washed with acetone and dried (4a, 8.7g, 60%). It did not show any depression in melting point when mixed with the bis(formamidino) sulphide dihydrochloride obtained in the above experiment.
Other compounds were also prepared in a similar fashion. In each case the product was identical with the corresponding one obtained from the thiourea-cyanamide reaction.

c) Chemical behaviour of bis(formamidino) sulphide dihydrochlorides

i) Reduction

Amidino-(N-n-butyl-N'-.n-propyl)amidino sulphide dihydrochloride (4a, 3g) was dissolved in ethanol and hydrogen sulphide was bubbled through the solution for 3 hrs. The solution was concentrated and diluted with water (10 ml) and cooled in ice. The colourless crystals which separated was collected (1.6g) and identified to be 1-n-butyl-3-n-propyl thiourea, m.p. and m.m.p. 48°. The filtrate was then treated with iodine in potassium iodide solution until the colour of iodine persisted. Aqueous picric acid was then added, the precipitate collected and repeatedly crystallised from dilute ethanol. The picrate was that of bis(formamidino) disulphide, m.p., 152° (lit.15 m.p. 154°).

The other sulphides also showed similar behaviour and they all gave the corresponding unsymmetrical 1,3-dialkylthioureas and thiourea on reduction.
ii) Oxidation

A solution of (4a) in ethanol was treated with hydrogen peroxide. Thiadiazole (7a) could not be isolated by work up.

iii) Decomposition in presence of sodium bicarbonate

An aqueous solution of amidino-(N-\(\text{n}\)-butyl-N-\(\text{\text{\textsuperscript{n}}\text{-butyl}}\) amidino sulphide dihydrochloride (4a), on treatment with saturated sodium bicarbonate solution decomposed to give an oil. It was extracted with ether and after removal of ether, the oil was treated with ammoniacal ethanol saturated with hydrogen sulphide. The alcoholic solution was concentrated and the viscous residue formed was dissolved in water (10 ml) and cooled in ice. The crystals which separated were collected and identified as 1-\(\text{n}\)-butyl-3-\(\text{n}\)-propylthiourea, by m.m.p. determination and also by t.l.c.

In the case of other bis(formamidino) sulphide salts also the corresponding 1-alkyl-3-benzylthioureas were formed.

iv) Isomerisation of bis(formamidino) sulphide dihydrochlorides: Formation of 1-amidino-1,3-dialkylthiourea hydrochlorides

Amidino-(N-\(\text{n}\)-butyl-N-\(\text{\text{\textsuperscript{n}}\text{-butyl}}\) amidino sulphide dihydrochloride (4a, 3g) was refluxed in ethanol for 2 hrs. The solution was then concentrated under reduced pressure.
No crystalline product could be isolated. It was then diluted with water and sodium bicarbonate was added to the solution and warmed. The butyl isothiocyanate formed was separated by steam distillation, treated with aqueous ammonia and cooled. 1-Butylthiourea (0.8g) crystallised out as shining needles, m.p. 79° during the concentration of the ammoniacal mixture. The other decomposition product, viz. n-propylguanidine could not be isolated even as its picrate from the residual solution left after the steam distillation.

The isomerised product from amidino-\((\text{N-benzyl-N'}\text{-methylamidino})\) sulphide dihydrochloride on similar decomposition gave benzyl isothiocyanate and methylguanidine. Benzylguanidine and related alkyl isothiocyanates were obtained when the other 1-alkyl-1-amidino-3-benzylthiourea hydrochlorides were decomposed with warm sodium bicarbonate solution.

v) Conversion to 4,5-dihydro-1,2,4-thiadiazole.

In another experiment, the solution obtained after refluxing the sulphide (4a, 3g) in ethanol was oxidised with hydrogen peroxide (2 ml, 30%). The solution was then cooled in ice and basified with aqueous ammonia. The solid which separated was collected (1.1g) and crystallised to constant
melting point, 90°C. This product showed no depression in melting point with an authentic sample of 3-amino-5-n-butylimino-4-n-propyl-4,5-dihydro-1,2,4-thiadiazole.

The other thiadiazoles were also prepared following the above procedure. They were all identical with the products obtained in the oxidation of binary mixtures of thioureas.
<table>
<thead>
<tr>
<th>Compound reduced</th>
<th>Intermediate amidinothiourea*</th>
<th>Thiourea obtained</th>
<th>M.p. &amp; m.m.p.°C</th>
<th>Guanidine (picrate) obtained</th>
<th>M.p. &amp; m.m.m.p.°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a g-Butyl</td>
<td>n-Propyl</td>
<td>n-Butyl</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7b Benzyl</td>
<td>Methyl</td>
<td>Benzyl</td>
<td>162</td>
<td>Methyl +</td>
<td>200</td>
</tr>
<tr>
<td>7c Ethyl</td>
<td>Benzyl</td>
<td>Ethyl</td>
<td>113</td>
<td>Benzyl ++</td>
<td>186</td>
</tr>
<tr>
<td>7d n-Propyl</td>
<td>&quot;</td>
<td>n-Propyl</td>
<td>110</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>7e Isopropyl</td>
<td>&quot;</td>
<td>Isopropyl</td>
<td>157</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>7f n-Butyl</td>
<td>&quot;</td>
<td>n-Butyl</td>
<td>79</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

* Not isolated.


++ See Ref.78.
<table>
<thead>
<tr>
<th>Reactants</th>
<th>Sulphide salt formed</th>
<th>M.p. °C</th>
<th>Found N%</th>
<th>S%</th>
<th>Required N%</th>
<th>S%</th>
</tr>
</thead>
</table>
| 1-
-Butyl-3-
-propylthiourea+cyanamide | C₉H₂₀N₄S·2HCl | 164 | 19.1 | 11.4 | 19.4 | 11.1 |
| 1-
-Butyl-3-
-propylcarbodiimide+thiourea | " | 182 | 19.2 | 11.4 | 19.4 | 11.1 |
| 1-Benzyl-3-methylthiourea+cyanamide | C₁₀H₁₄N₄S·2HCl | 160 | 18.9 | 10.7 | 18.8 | 11.0 |
| 1-Benzyl-3-methylcarbodiimide+thiourea | " | 161 | 18.8 | 10.8 | 18.8 | 10.8 |
| 1-Benzyl-3-ethylthiourea+cyanamide | C₁₁H₁₆N₄S·2HCl | 181 | 18.1 | 10.5 | 18.1 | 10.4 |
| 1-Benzyl-3-ethylcarbodiimide+thiourea | " | 180 | 17.8 | 10.0 | 18.1 | 10.4 |
| 1-Benzyl-3-n-propylthiourea+cyanamide | C₁₂H₁₈N₄S·2HCl | 172 | 17.6 | 10.1 | 17.3 | 9.9 |
| 1-Benzyl-3-n-propylcarbodiimide+thiourea | " | 172 | 17.4 | 9.6 | 17.3 | 9.9 |
| 1-Benzyl-3-isopropylthiourea+cyanamide | C₁₂H₁₈N₄S·2HCl | 165 | 17.4 | 10.0 | 17.3 | 9.9 |
| 1-Benzyl-3-isopropylcarbodiimide+thiourea | " | 167 | 17.1 | 9.6 | 17.3 | 9.9 |
| 1-Benzyl-3-n-butylthiourea+cyanamide | C₁₃H₂₀N₄S·2HCl | 188 | 16.4 | 9.6 | 16.6 | 9.5 |
| 1-Benzyl-3-n-butylcarbodiimide+thiourea | " | 188 | 16.3 | 9.0 | 16.6 | 9.5 |